Nefecon treatment response in Asian and White patient populations with immunoglobulin A nephropathy: A 2-year analysis of the Phase 3 NefIgArd trial

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Nefecon has not been approved by the Japanese Pharmaceuticals and Medical Devices Agency.

The 17th International Symposium on IgA nephropathy

COI disclosure

Presenter: Jonathan Barratt

I have the following relationships to disclose any COI for this research presentation within the period of 36 months.

- **Employment/leadership position/advisory role: Calliditas Therapeutics**
- **Stock ownership or options:**
- **Patent royalties/licensing fees:**
- **Honoraria (e.g. lecture fees):**
- **Manuscript fees:**
- **Research funding: Calliditas Therapeutics**
- **Subsidies or donations:**
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- **Travel fees, gifts, and others:**

COI, conflict of interest

Introduction

- Nefecon is a novel, oral, targeted-release budesonide formulation specifically designed to treat IgAN by inhibiting IgA formation in the Peyer's patch-rich distal ileum[1,2]
- In the interim analysis of the Phase 3 NefIgArd trial, treatment of patients with primary IgAN with Nefecon 16 mg/day for 9 months resulted in significantly reduced proteinuria and eGFR benefit compared with placebo at 3 months post treatment[3]
- People of East Asian ancestry have the highest likelihood of all race categories to progress to kidney failure as a result of IgAN[4]
- Here, we present the overall safety and efficacy data from the full 2-year NefIgArd trial (9 months of treatment and 15 months off-treatment follow-up) and assess responses to Nefecon in patients identifying as Asian or White

eGFR, estimated glomerular filtration rate; IgA, immunoglobulin A, IgAN, immunoglobulin A nephropathy; UPCR, urine protein-creatinine ratio.

1. Barratt J, *et al. Kidney Int Rep* 2020;5:1620-1624. 2. Calliditas Therapeutics press release. March 12, 2023. https://www.calliditas.se/en/calliditas-announces-primary-endpoint-successfully-met-in-phase-3-nefigard-trial-evaluating-nefecon-in-iga-nephropathy/ (accessed September 2023). 3. Barratt J, *et al. Kidney Int* 2022;103:391-402.
4. KDIGO Glomerular Diseases Work Group. *Kidney Int* 2021;100:S1-S276.

Methods

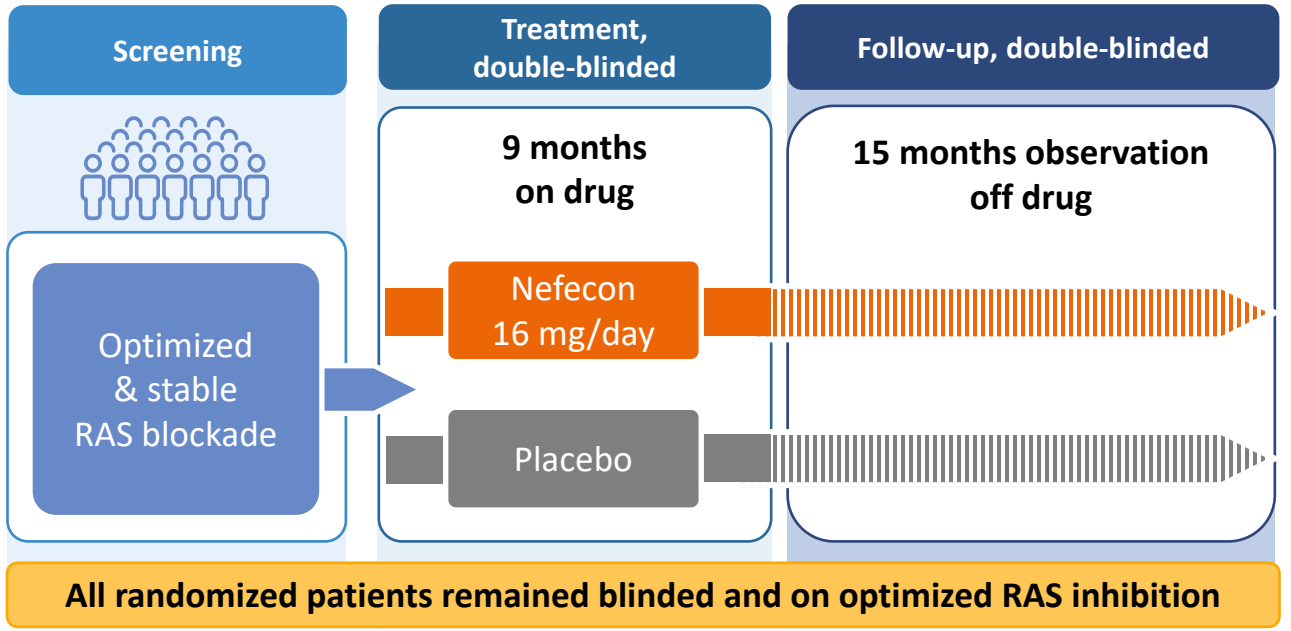
NefIgArd: A Phase 3, two-part, randomized, double-blind, placebo-controlled study

Key inclusion criteria:

- ≥18 years old with biopsy-confirmed primary IgAN
- UPCR ≥0.8 g/g or proteinuria ≥1 g/24 h, despite optimized RAS inhibitor blockade
- eGFR 35-90 mL/min/1.73 m²

Key exclusion criteria

- Secondary form of IgAN or non-IgAN glomerulonephritis
- Kidney transplant
- Systemic diseases that may cause mesangial IgA deposition
- Poorly controlled BP (≥140/90 mmHg)
- Poorly controlled T1D or T2D



Subgroup analysis by race

- Time-weighted eGFR average over 2 years, changes in UPCR and UACR, time to 30% reduction in eGFR or kidney failure, microhematuria, and safety outcomes were stratified according to whether patients identified as Asian or White
  - Race categories were defined based on those specified by the FDA
- Full analysis set included 364 patients: Asian (n=83), White (n=275), and other (n=6)

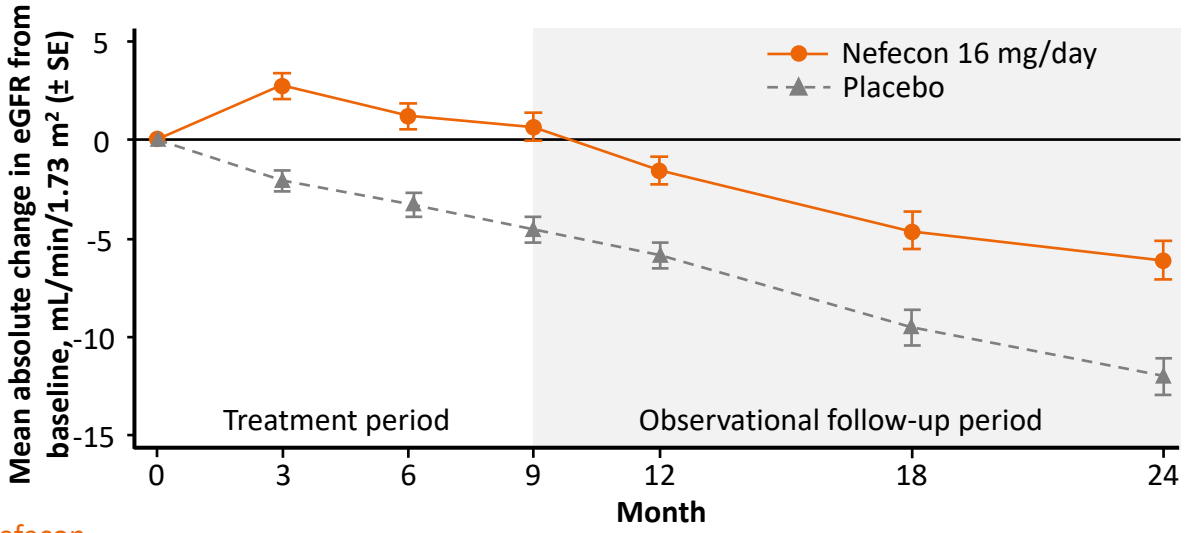
BP, blood pressure; eGFR, estimated glomerular filtration rate; FDA, US Food and Drug Administration; Ig, immunoglobulin; IgAN, immunoglobulin A nephropathy; RAS, renin–angiotensin system; T1D, type 1 diabetes; T2D, type 2 diabetes; UACR, urine albumin-creatinine ratio; UPCR, urine protein-creatinine ratio.

Overall study population: Key efficacy results

For additional details on the primary results from NeflgArd please scan here:

Primary endpoint: Time-weighted average change from baseline in eGFR over the 2-year period

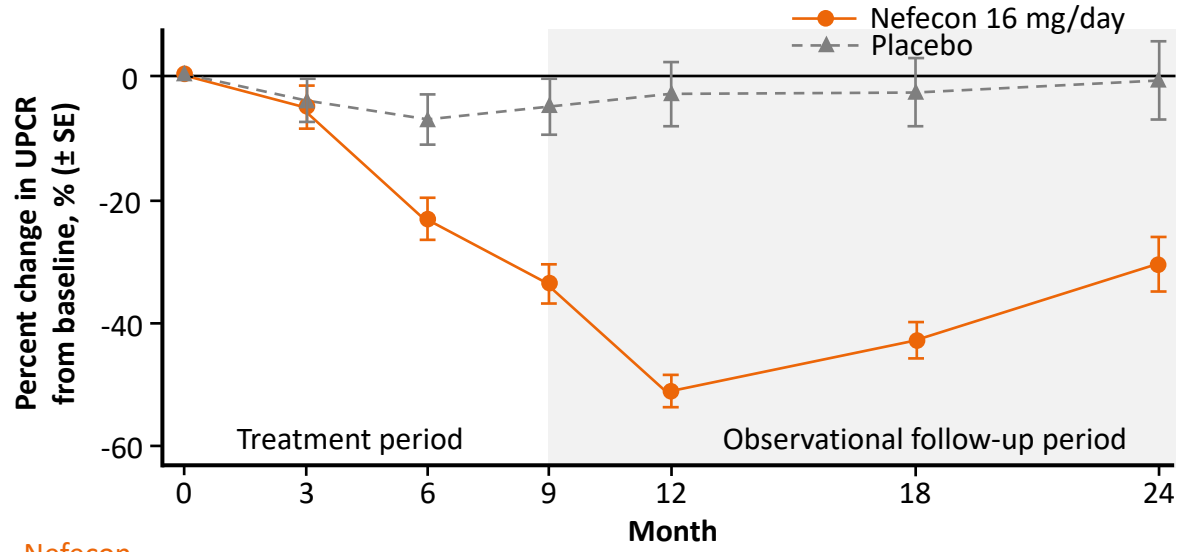
eGFR treatment benefit of **5.1** (95% CI 3.2, 7.4) mL/min/1.73 m^2 with Nefecon 16 mg/day vs placebo (p<0.0001)



Nefecon 16 mg, n	182	171	167	167	153	155	149
Placebo, n	182	178	171	164	161	150	146

Secondary endpoint: Mean percentage change in UPCR from baseline

30% reduction in UPCR with Nefecon compared with placebo observed after the 9-month treatment period **sustained up to 2 years**



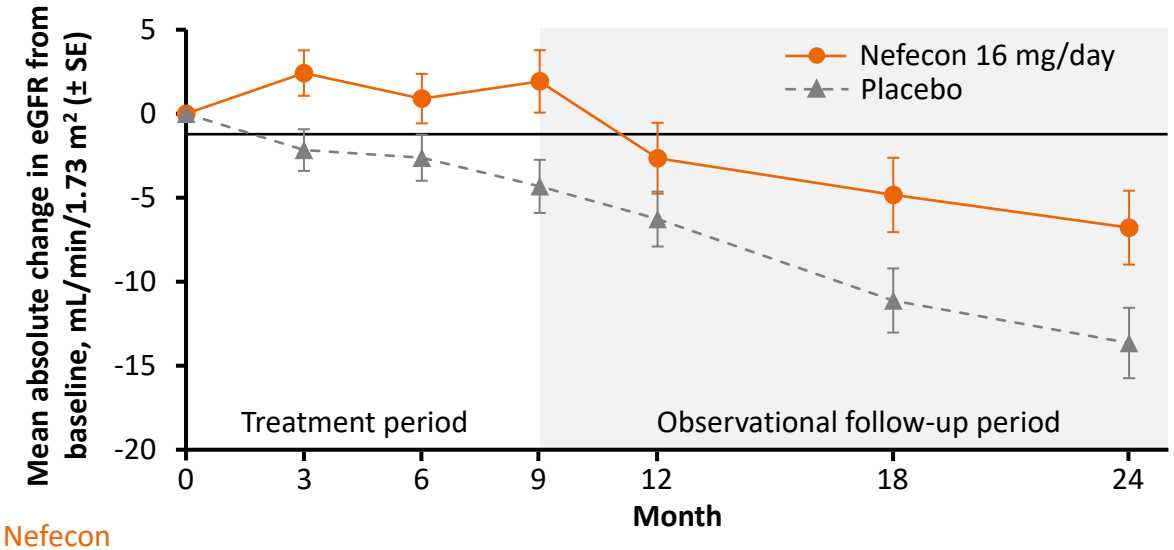
Nefecon 16 mg, n	182	173	169	166	157	155	145
Placebo, n	182	176	169	164	160	151	142

CI, confidence interval; eGFR, estimated glomerular filtration rate; SE, standard error; UPCR, urine protein-creatinine ratio.

Race subgroup analysis: 2-year time-weighted average eGFR

Asian patients

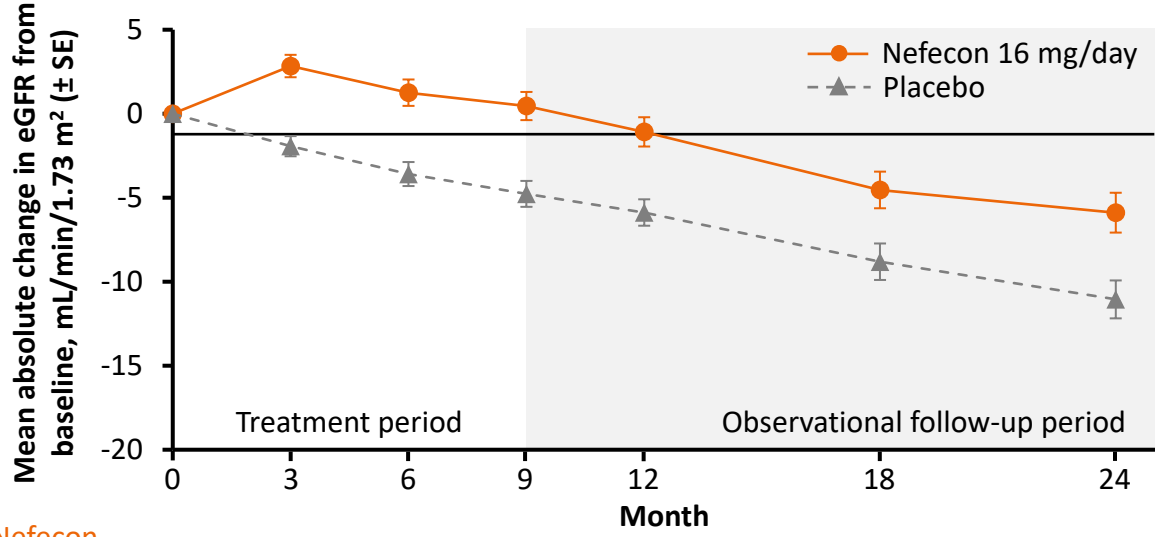
Primary endpoint
Time-weighted average change in eGFR over the 2-year period
Difference of **5.5** mL/min/1.73 m^2 (95% CI 1.4, 9.9) **in favor of Nefecon***



Nefecon 16 mg, n	43	39	35	37	35	31	31
Placebo, n	40	40	37	37	36	31	29

White patients

Primary endpoint
Time-weighted average change in eGFR over the 2-year period
Difference of **4.8** mL/min/1.73 m^2 (95% CI 2.4, 7.3) **in favor of Nefecon***



Nefecon 16 mg, n	138	131	131	129	117	123	117
Placebo, n	137	133	129	122	121	116	114

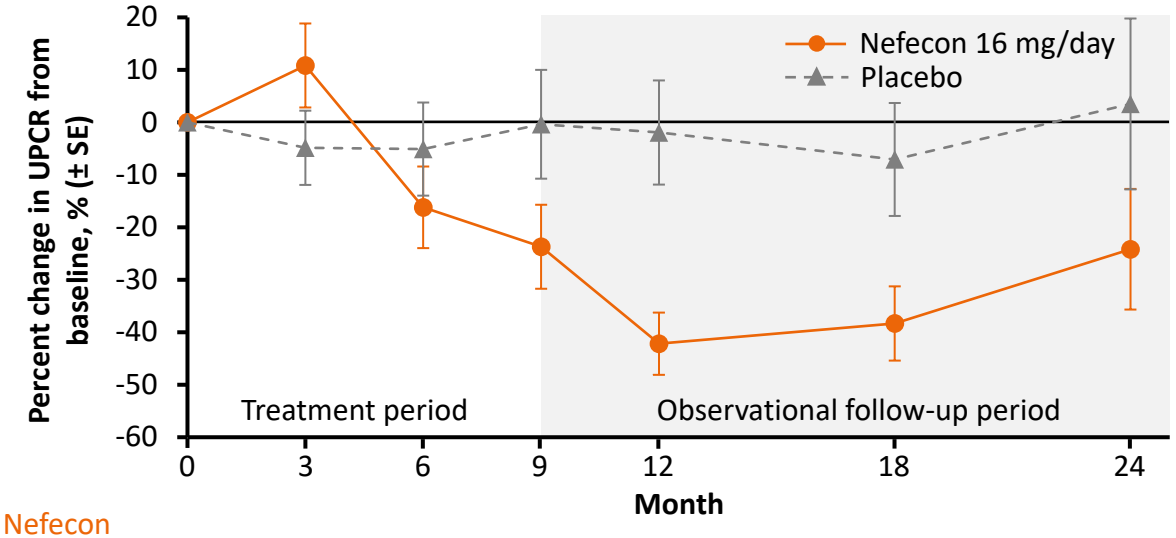
*Calculated based on the difference between pooled baseline geometric mean × (geometric LS mean of ratio of AUC over 2 years compared with baseline for each treatment arm – 1) for Nefecon minus placebo.
CI, confidence interval; eGFR, estimated glomerular filtration rate; SE, standard error.

Race subgroup analysis: UPCR

Asian patients

Secondary endpoint: Estimated percent reduction from baseline in UPCR*

- Greater percent reduction from baseline in UPCR for Nefecon vs placebo at **9 months (23%)** and **24 months (27%)**

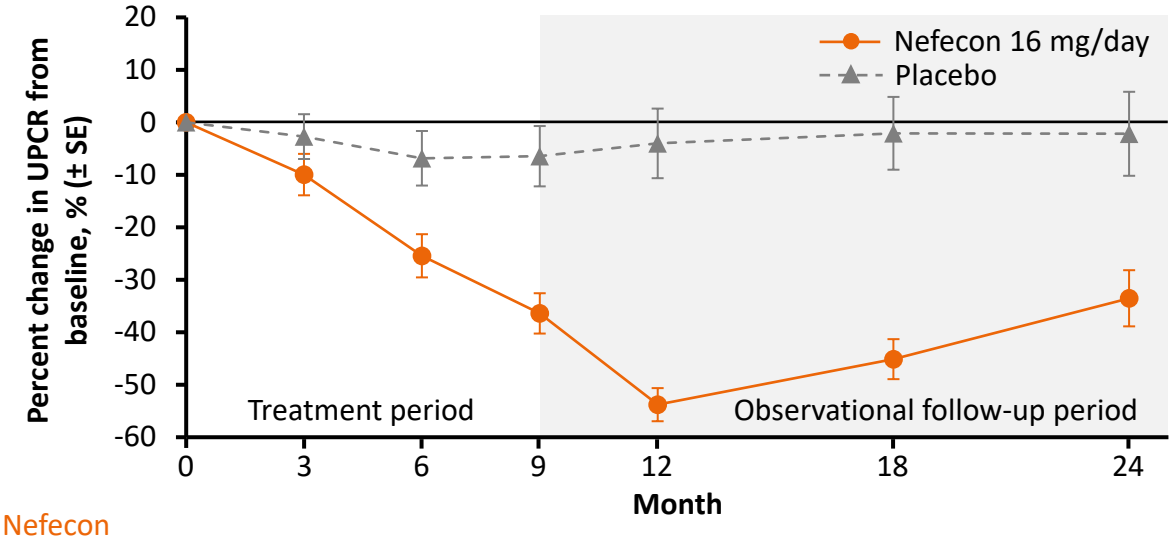


Nefecon 16 mg, n	43	42	37	36	35	31	31
Placebo, n	40	40	38	38	37	31	29

White patients

Secondary endpoint: Estimated percent reduction from baseline in UPCR*

- Greater percent reduction from baseline in UPCR for Nefecon vs placebo at **9 months (32%)** and **24 months (32%)**



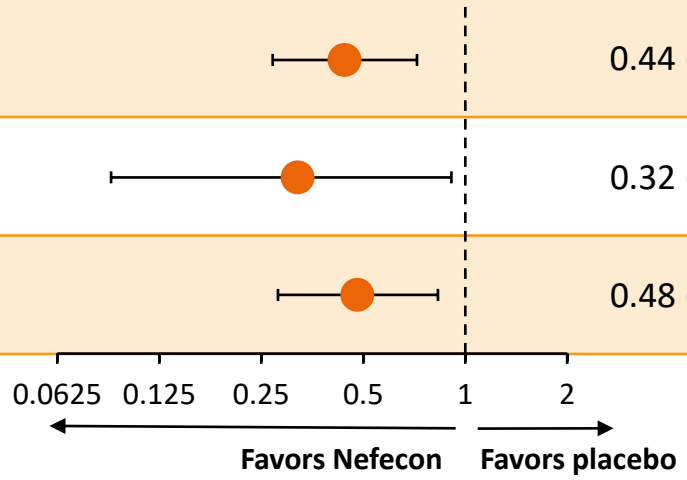
Nefecon 16 mg, n	138	130	131	129	121	123	113
Placebo, n	137	131	127	122	119	117	110

*For each postbaseline visit, the geometric mean of all available measurements within the corresponding analysis window was used.
SE, standard error; UPCR, urine protein-creatinine ratio.

Race subgroup analysis: 30% reduction in eGFR or kidney failure

First confirmed 30% reduction in eGFR or kidney failure regardless of rescue medication

	Nefecon n/n (%)	Placebo n/n (%)	HR (95% CI)	p-value
All patients (N=364)	25/182 (14%)	49/182 (27%)	0.44 (0.27-0.71)	0.0009
Asian patients (N=83)	4/43 (9%)	13/40 (33%)	0.32 (0.09-0.91)	0.0479
White patients (N=275)	21/138 (15%)	34/137 (25%)	0.48 (0.28-0.83)	0.0093



Nefecon significantly reduced the risk of 30% reduction in eGFR or kidney failure irrespective of whether patients were Asian or White

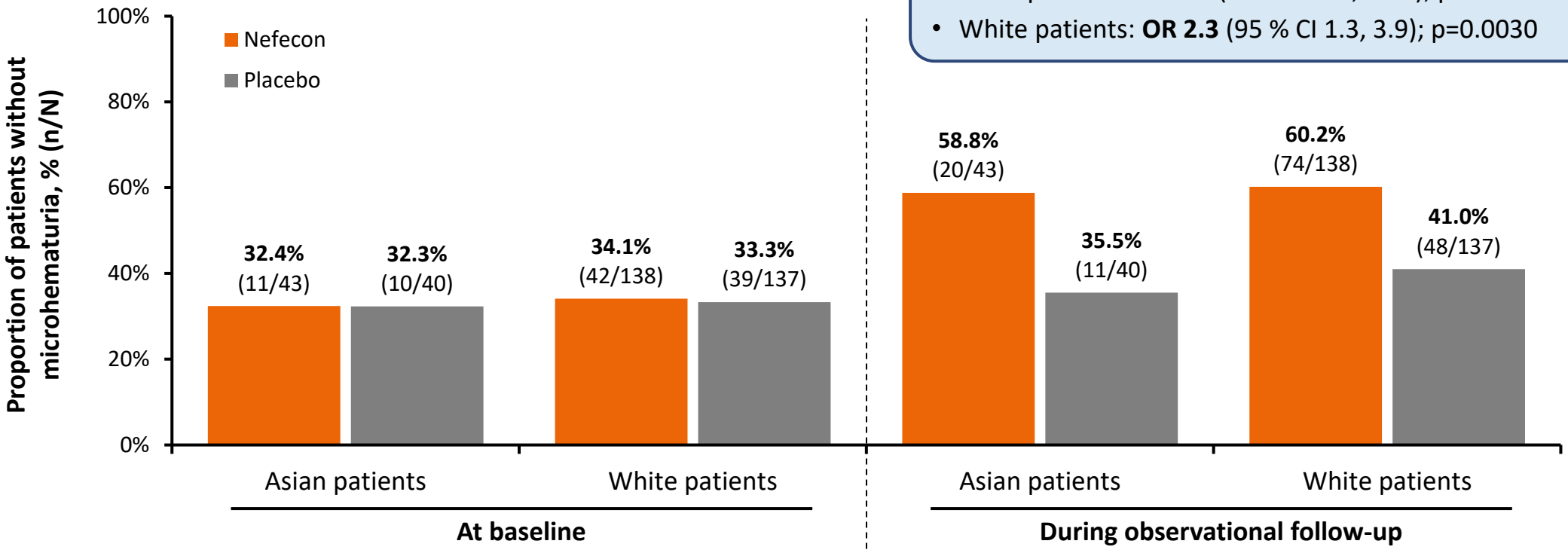
This was a post hoc analysis using an unweighted Cox model, in which the time to confirmed 30% eGFR reduction was estimated regardless of use of rescue medication. 30% reduction in eGFR was confirmed by two values over ≥4 weeks and kidney failure was defined as dialysis, kidney transplantation, sustained eGFR <15 mL/min/1.73 m², or kidney-related death.
CI, confidence interval; eGFR, estimated glomerular filtration rate.

Race subgroup analysis: Microhematuria

Proportion of Asian and White patients without microhematuria* at baseline and observational follow-up, stratified by race

Comparison of Nefecon 16 mg/day vs placebo:

- Asian patients: **OR 3.5** (95 % CI 1.2, 11.7); p=0.0303
- White patients: **OR 2.3** (95 % CI 1.3, 3.9); p=0.0030



*A patient was defined as without microhematuria if the urine dipstick returned a result of negative or trace. Patients without at least two valid results from 12 months onwards were excluded from the analysis.

CI, confidence interval; OR, odds ratio.

Race subgroup analysis: Safety

- Rates of TEAEs were **broadly similar** across groups, although with a slightly higher overall rate of TEAEs in **Asian** patients
- Compared with White patients, Asian patients receiving Nefecon were:*
  - **More likely** to experience peripheral edema, face edema, and arthralgia
  - **Less likely** to experience muscle spasms, acne, headache, and fatigue
- Rates of infections, diabetes, and hypertension **were broadly similar** among White and Asian patients

	Asian (N=83)		White (N=275)	
	Nefecon, n (%) (n=43)	Placebo, n (%) (n=40)	Nefecon, n (%) (n=138)	Placebo, n (%) (n=137)
All TEAEs	43 (100)	29 (72.5)	115 (83.3)	92 (67.2)
Mild	22 (51.2)	19 (47.5)	71 (51.4)	53 (38.7)
Moderate	20 (46.5)	10 (25.0)	36 (26.1)	36 (26.3)
Severe	1 (2.3)	0 (0)	8 (5.8)	3 (2.2)
Any serious TEAEs	4 (9.3)	0 (0)	14 (10.1)	8 (5.8)
Any treatment-related serious TEAEs	3 (7.0)	0 (0)	1 (0.7)	4 (2.9)
Any AEs leading to death	0 (0)	0 (0)	1 (0.7)	0 (0)
Any TEAEs leading to discontinuation of study treatment	7 (16.3)	0 (0)	10 (7.2)	3 (2.2)

*Based on AEs which occurred in ≥5% of patients in the Nefecon arm (overall population) and were higher than for placebo recipients.
AE, adverse event; TEAE, treatment-emergent adverse event.

Discussion

- The NefIgArd study successfully **met its 2-year primary endpoint**, demonstrating 9 months of Nefecon treatment provided a statistically significant and clinically relevant **preservation of eGFR** compared with placebo
  - Nefecon achieved a **durable reduction in proteinuria** when evaluated 15 months after end of treatment
  - Nefecon was also **well tolerated**, with a safety profile as expected for a locally acting oral budesonide product
- Although the number of patients identifying as Asian was considerably lower than the number identifying as White, the results from this subgroup analysis indicate that Nefecon was efficacious and well tolerated **irrespective of White or Asian race**

eGFR, estimated glomerular filtration rate.